REMARKS

Status of the Claims

Claims 45-49, 51, 53-62 and 65-68 are pending in the instant application. Claims 45, 47, 61 and 62 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications. Claims 46, 48, 49, 51, 53-60 and 65-68 are currently being examined on the merits.

Applicants also respectfully remind the Examiner that Claims 47, 61 and 62 are "method of use" claims which all ultimately depend from product claim 46. Therefore, upon allowance of claim 46, it is believed that Claims 47, 61 and 62 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)."

Objection to the Specification

The Examiner objected to the Specification for allegedly not providing antecedent basis for the claimed matter, in particular for the recitation of "a polypeptide having a naturally-occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO:1" in claim 46.

Such, however is not the case. The support is described throughout the specification of the instant application, for example, at page 3, lines 20-26, page 4, lines 27-29, page 8, lines 26-30, page 9, lines 1-4 and lines 13-28, page 10, lines 7-11, and page 31, lines 9-12.

For at least the above reasons, withdrawal of this objection is respectfully requested.

Utility rejection under 35 U.S.C. § 101

Claims 46, 48, 49, 51, 53-60 and 65-68 were rejected under 35 U.S.C. § 101 based on the allegation that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. This rejection is respectfully traversed. The rejection of claims 46, 48, 49, 51, 53-60 and 65-68 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

In this rejection, the Office Action focuses on the alleged lack of utility of the polypeptides which are specifically bound by the claimed antibodies. Based on this alleged lack of utility of the polypeptides, the Office Action asserts that the only use for the claimed antibodies is to carry out further research on the polypeptides specifically bound by the antibodies. However, the Office Action is incorrect in asserting that "further research would be required to identify or reasonably confirm a "real world" context of use, for example, to identify any function of NTPPH-2 and conditions for which NTPPH-2 polypeptides, fragments and "naturally occurring" 90% identical polypeptides would be of diagnostic or therapeutic significance." (Office Action, page 5). The claimed antibodies have specific, substantial, and credible utilities in, for example, the purification and/or detection of polypeptides. It is the polypeptides which are the object of further research, not the claimed antibodies. In these methods, the claimed antibodies are tools which facilitate research on the polypeptides. For example, purification of polypeptides using the claimed antibodies has the useful benefit of providing the polypeptides in a form suitable for further research on the polypeptides. In another example, detection of polypeptides using the claimed antibodies has the useful benefit of monitoring the presence and/or amount of the polypeptides during research on the polypeptides. In such methods, the claimed antibodies are a research tool, and therefore have specific, substantial, and credible utilities.

Much of the Office Action's argument focuses on the alleged lack of utility of the polypeptides which are specifically bound by the claimed antibodies. For example, the Examiner asserts that:

> "without a "real world' use for the protein, antibodies specific therefore are equally not useful, as basic research such as studying the properties of the product of the polypeptide are not considered substantial and credible utility for the claimed invention. Therefore, the specification does not fairly disclose a substantial and credible utility for the antibody of the instant claims." (Office Action, page 5)

and that:

> "The instant specification does not provide any information about the structure of the predicted NTPPH-2 polypeptide, only sequence identity to the porcine

nucleotide pyrophosphohydrolase NTPPH, and for this reason the specification provides insufficient information to enable the artisan to reasonably predict that NTPPH-2 is functionally related to NTPPH and therefore the specification does not teach the artisan a credible utility for NTPPH-2." (Office Action, page 5)

However, the claims at issue are drawn to **antibodies**. The claimed antibodies have specific, substantial, and credible utilities in, for example, the purification and/or detection of polypeptides. It is improper for the Patent Office to base the instant rejection on the alleged lack of utility of the recited polypeptides because the claims are drawn to the recited antibodies, not to the recited polypeptides. Nevertheless, in the interest of providing a complete response to the Office Action's arguments, Applicants address the utility of the claimed antibodies based on the specific, substantial, and credible utilities of the recited polypeptides, below.

The invention at issue, identified in the patent application as an antibody to NTPPH-2, is an antibody to a polypeptide encoded by a gene that is expressed in cartilage, testes, trachea and bone marrow. The NTPPH-2 gene can be identified by membrane-based northern analysis and is expressed in libraries which are involved in immunological responses, many of which are cartilage or joint related and is present in immortalized or cancerous cells and tissues of humans (Specification, e.g., at page 16, lines 24-29). The novel polypeptide NTPPH-2 is demonstrated in the specification to be a member of the nucleotide pyropshosphohydrolase family (e.g., at page 15, lines 27-28), whose biological functions include hydrolyzing nucelotide triphosphates and release PPi (e.g., at page 2, line 7). The claimed antibody has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide bound by the claimed antibody actually functions biologically. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the polypeptide bound by the claimed antibody is a member of the nucleotide pyropshosphohydrolase family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, is useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the polypeptide bound by the claimed antibody also has patentable utility, regardless of its actual

function. The law has never required a patentee to prove more. Analogously, the claimed antibody also has patentable utility, as it can be used, *inter alia*, to purify and detect the polypeptide to which it specifically binds.

Applicants further submit with this Response three expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references. The Rockett Declaration, Bedilion Declaration, Iyer Declaration, and the ten (10) references fully establish that, prior to the December 22, 1997 filing date of the Application Serial Number 08/996,083 (Magna, '083) application, it was well-established in the art that:

> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;
>
> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;
>
> antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;
>
> failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and
>
> failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in

that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

a. The Office Action misapplies and distorts the teachings of Brenner et al. regarding the reliability of sequence identity in predicting functional similarity

The Examiner cites the Brenner et al. article identifying some of the difficulties that may be involved in predicting protein function. However, nothing in that document suggests that functional homology cannot be inferred by a reasonable probability in this case. Importantly, nothing contradicts Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, the Brenner article stands for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

The Office Action also misinterprets the teachings of Brenner et al. Brenner et al. discuss the reliability of assignment of structural and functional relationships between known sequences and homologous ones. Through exhaustive analysis of a dataset of proteins with known structural and functional relationships, Brenner et al. have determined that 40% identity is a reliable threshold when aligned over at least 70 residues (Brenner, pages 6073 and 6076). This evidence should have been more than sufficient to end discussion of the credibility, to the degree required by 35 U.S.C. §§ 101 and 112, first paragraph, of Applicants' assignment of function to the claimed polypeptide.

The Office Action cites caveats in Brenner et al. which discuss how such results might be skewed (**not** rendered unreliable) by the selection of sequences in the database. The Office Action further cites Brenner's discussion of other useful information relating to structure which can be used to supplement (**not** to replace) the sequences comparisons, and then misconstrues the clear meaning of Brenner's statement that "comparing structures is a more powerful (if less convenient) way to recognize distant evolutionary relationships than comparing sequences" to

imply that there is something improper or unreliable about comparing sequences. This is a plainly incorrect interpretation of Brenner's statement. Brenner's statement clearly points to the fact that sequence comparisons are **limited** in their ability to identify some distant relationships that can be better seen using structural comparisons – the clear conclusion being that sequence comparisons **under-identify** (and thus miss) actual structure/function relationships rather than misidentify them. In fact, the Office Action completely ignores the quote taken from the Abstract of the paper that sums up the teaching of this reference: "**Because many homologs have low sequence similarity, most distant relationships cannot be detected by any pairwise comparison method; however *those which are identified may be used with confidence*".** (Emphasis added.) Nothing the Office Action asserts addresses this fundamental teaching of this reference. Clearly, the 50% sequence identity between the known nucleotide pyrophosphohydrolase (NTTP-1) and the claimed novel NTTP-2 is a credible basis for Applicants' assertion of utility.

b. The Patent Office has not met its burden of making a *prima facie* case for lack of utility

The Office Actions's factual and scientific arguments are neither adequately supported nor do they rise to the level of adequacy necessary to overcome the presumption of objective truth of Applicants' assertions of utility and enablement.

Applicants first reiterate their primary position, which is that the Patent Office has failed in the first place to establish a proper *prima facie* case of lack of utility or enablement sufficient to shift the burden to Applicants to overcome, and that therefore, no rebuttal of this rejection should ever have been necessary. The Office Action's mere expression of doubt regarding the reliability of homology-based assignment of function (and thus use) is insufficient to support the necessary conclusion that one of ordinary skill in the art, reading Applicants' specification and claims, together with any evidence or sound scientific reasoning supplied by the Office Action, would doubt the veracity of Applicants' asserted use, i.e., that the skilled worker would find it more likely than not that the asserted utility and enabling disclosure was wrong and inoperable. It is only if that initial burden belonging to the Patent Office is met that the burden of proof of utility and enablement shifts to the Applicants.

In any case, the evidence proffered to support the contention that the skilled worker would doubt the veracity of Applicants' asserted use(s) is inadequate to meet this initial burden,

as discussed above.

In addition, it is noted that, according to recent conversations with supervisory personnel in Technology Center 1600 of the USPTO, this aspect of the argument regarding the credibility of homology-based assertion of function has been discredited.

In fact, at a recent Biotechnology Customer Partnership Meeting held at the USPTO on April17, 2001, in a talk by Senior Examiner James Martinell, it was emphasized that Applicant's assertion that his claimed protein "is a member of a family of proteins that is already known based upon amino acid sequence homology" can be effective as an assertion of utility for the claimed sequence. According to Dr. Martinell, the proper question for the Examiner to ask, after searching the prior art for the claimed protein, is "Would one of skill in the art accept that the protein has been placed in the correct family of proteins as is asserted?" The "two" [sic: three] possible answers that can be deduced from this prior art search are, according to Dr. Martinell:

- The search does not reveal any **evidence** that the family attribution made in the application is either **incorrect or may be incorrect**
- The protein either **more likely belongs to a family other than that asserted** in the application or **likely does not belong to the family asserted** in the application
- The search shows that the attribution is likely correct

(From handouts of Dr. Martinell's slides distributed April 17, 2001; emphasis added)

It is clear from the above that the tactic taken by the Examiner in asserting the very slight possibility that ANY minor sequence change might have a dramatic effect on the function of the protein has been abandoned by the USPTO as a credible basis for a rejection under either the utility requirement of 35 U.S.C. § 101 or the enablement requirement of §112, first paragraph.

However, in any case, it is noted that the Office Action has failed to meet the above requirements now recognized by the USPTO. The Office Action has cited no evidence particular to the claimed protein, e.g., inconsistent findings deduced from a search, upon which to base any objection to the assignment of functional homology to the family of nucleotide pyrophosphohydrolase proteins. Indeed, there is no such evidence.

Moreover, it must be remembered, as set forth in the USPTO's own M.P.E.P. § 2107, that in order to raise such doubt in the veracity of Applicants' assertion, the Office Action must establish either (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. The Office

Action has accomplished neither of these minimum standards.

In any event, as demonstrated by the Rockett Declaration, the Bedilion Declaration and the Iyer Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene and protein expression monitoring applications including toxicology testing are in fact independent of its precise function.

While it is true that all polypeptides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific, substantial, and credible. A toxicology test using any particular expressed polypeptide is dependent on the **identity** of that polypeptide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polypeptide in toxicology testing is specific to both the compound being tested and the polypeptide used in the test. No two human-expressed polypeptides are interchangeable for toxicology testing because the effects on the expression of any two such polypeptides will differ depending on the identity of the compound tested and the **identities** of the two polypeptides. It is not necessary to know the biological functions and disease associations of the polypeptides in order to carry out such toxicology tests. Therefore, it is not necessary to show that the polypeptides bound by the claimed antibodies are "associated with the etiology of a disorder of cellular proliferation" in order for the claimed antibodies to have a specific and substantial utility in toxicology testing. At the very least, the polypeptides bound by the claimed antibodies are specific controls for toxicology tests in developing drugs targeted to other polypeptides, and are clearly useful as such.

Furthermore, because any expressed polypeptide can be used as a specific control in a toxicology test for developing drugs targeted to other polypeptides, the claimed antibodies which specifically bind to the recited polypeptide variants of SEQ ID NO:1 have utilities that meet the requirements of 35 U.S.C. § 101. The recited polypeptide variants of SEQ ID NO:1 have naturally occurring amino acid sequences. It is useful to know if the expression of any such polypeptide is altered in response to exposure to an exogenous compound such as a drug candidate targeted to another polypeptide. This is true even if one does not know the biological functions or disease associations of a polypeptide used in such a toxicology test. Therefore, the

recited polypeptide variants of SEQ ID NO:1, and antibodies which specifically bind to them, have utilities that meet the requirements of 35 U.S.C. § 101. Insofar as the arguments below apply to the specific and substantial utilities of antibodies to the SEQ ID NO:1 polypeptide which are due to the expression of the SEQ ID NO:1 polypeptide in naturally occurring tissues, these same arguments also apply to antibodies to polypeptide variants of SEQ ID NO:1 having naturally occurring amino acid sequences.

For at least the above reasons, withdrawal of this rejection is respectfully requested.

Enablement Rejection Under 35 U.S.C. § 112, first paragraph

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Office Action, page 6). To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

In addition, Claims 46, 48, 49, 51, 53-60 and 65-68 were rejected as failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide sufficient guidance to enable the skilled artisan to make and use the claimed antibodies. In particular, the Examiner asserts that "there is insufficient guidance in the specification as-filed to direct a person skilled in the art as to how to make and use antibodies to a polypeptide comprising a "naturally occurring" amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 even wherein said naturally-occurring amino acid sequence has nucleotide pyrophosphohydrolase activity" (Office Action, page 6). The Examiner does not dispute that the present application describes how to make an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or to an immunogenic fragment of SEQ ID NO:1.

The Office Action does not appear to dispute that conventional methods for making antibodies could be used to make antibodies which specifically bind to a polypeptide comprising a naturally occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO:1. Instead, the Office Action asserts that the present disclosure is deficient because one of skill in the art would not be able to make the variant polypeptides of SEQ ID NO:1 *per se* and, hence, without the variant polypeptides, one would not be able to make

antibodies which specifically bind to those variant polypeptides.

Applicants respectfully traverse. Antibodies which specifically bind to a polypeptide can be made as long as that polypeptide, or fragments thereof, are available; there is no restriction on the amino acid sequence of polypeptides that can be used to make antibodies. Since a polypeptide having **any** naturally occurring amino acid sequence that is 90% identical to SEQ ID NO:1 can be used to make antibodies using the methods disclosed in the Specification, it is not necessary to identify particular naturally occurring amino acid sequences that are 90% identical to SEQ ID NO:1 that could be used in this manner.

The Specification discloses how to make both the polypeptides themselves and the antibodies which specifically bind the polypeptides.

a. Making the Polypeptides

The Specification enables the making of the SEQ ID NO:1 polypeptides. (See, e.g., Sequence Listing and Specification, page 15, lines 16-24 and pages 58 to 60.)

Applicants submit that the Specification also enables the making of the polypeptide variants to which the claimed antibodies specifically bind. The polypeptide sequence of SEQ ID NO:1 is provided in the Sequence Listing. The claims define the variant polypeptides as "naturally occurring" and being at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having nucleotide pyrophosphohydrolase activity. The choice of amino acids to alter is made by nature. They are not created exclusively in a laboratory. Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of NTPPH-2) and SEQ ID NO:2 (the polynucleotide sequence encoding NTPPH-2), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application, for example, at page 8, lines 9-25, page 9, lines 5-8, page 12, lines 18-26, page 14, lines 13-29 and Example VI at pages 51-53.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only

screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims. Therefore, the recited polypeptide variants and fragments are fully described in the specification.

b. Making the Antibodies

Applicants submit that the Specification enables the making of the claimed antibodies. See e.g., page 30, lines 23 through page 32, line 15. The Examiner misapprehends the plain meaning of the claims. The claims are directed to isolated antibodies which ***specifically bind*** to the protein -- if the antibody doesn't specifically bind, then it is not encompassed by the claim.

Further, the Examiner misapplies the law. To enable the claimed invention, Applicants need only disclose information sufficient to permit one of ordinary skill in the art to make and use the invention as claimed, without *undue* experimentation. It is the Examiner's burden to establish that undue experimentation would be necessary to carry out Applicants' invention. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

The specification discloses methods to make antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence (e.g., at page 30, line 15 through page 32, line 15; and page 55, line 28 through page 56, line 12). Given the information provided by SEQ ID NO:1 (the amino acid sequence of NTPPH-2), one of skill in the art would be able to routinely obtain antibodies which specifically bind to any of the recited variants and fragments of SEQ ID NO:1, including a polypeptide comprising "a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity," a polypeptide comprising "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has pyrophosphohydrolase activity," and a polypeptide comprising "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." For example, an animal could be immunized with any of the recited variants and fragments of SEQ ID NO:1, antibodies could be isolated from the animal, and the antibodies could be screened to identify

antibodies which specifically bind to the polypeptide.

Likewise, the specification discloses methods to use antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence in, for example, the purification of such polypeptides (e.g., at page 56, lines 14-24), the detection and/or measurement of such polypeptides (e.g., at page 26, line 25 through page 27, line 3; and page 38, line 14 through page 39, line 5), and the competitive screening of drug candidates (e.g., at page 46, lines 27-30). Given the information provided by SEQ ID NO:1, one of skill in the art would be able to routinely use antibodies which specifically bind to any of the recited variants and fragments of SEQ ID NO:1, including a polypeptide comprising "a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity," a polypeptide comprising "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity," and a polypeptide comprising "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." For example, an antibody which specifically binds to any of the recited variants and fragments of SEQ ID NO:1 could be coupled to an activated chromatographic resin, and this resin could then be used in an immunoaffinity column to purify the polypeptide.

Furthermore, the Specification, e.g., at page 30, lines 23 through page 32, line 15 and pages 55-56, describes methods well known in the art for making antibodies to the polypeptides and polypeptide fragments of the present invention, which methods include but are not limited to the production of monoclonal antibodies, polyclonal antibodies, chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, and humanized antibodies. With respect to monoclonal antibody production, the Specification describes a number of techniques known in the art for producing them, including the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. References detailing the particulars of those techniques are incorporated into Applicants' Specification. Also included in the disclosure are screening methods for identifying antibodies having the desired specificity.

In general, antibody production is an empiric process that necessarily requires immunization with particular putative immunogenic fragments and subsequent screening of the

products (e.g. antisera, hybridoma supernatants, recombinant immunoglobulin libraries or panels of highly specific binding reagents) to identify those fragments capable of giving rise to antibodies having the requisite specificity and affinity for the target antigen (in the present case, SEQ ID NO:1). This procedure is routine in the art, and does not constitute undue experimentation which would render Applicants' invention not enabled. See, e.g., *In re Wands* 8USPQ 2d 1400 (CAFC 1988). Indeed, the generation of antibodies necessarily involves genetic rearrangement in reaction to immunogenic challenge; that rearrangement process, and the resulting products, are inherently variable and constitute the basis for the remarkable ability of the mammalian immune system to respond to novel antigenic challenges with a high degree of specificity. Therefore, the process of challenge and screening are an inherent and unavoidable part of identifying immunogenic fragments, and cannot be considered undue experimentation.

In addition, the Examiner's assertions are irrelevant because it is not necessary to predict what changes in SEQ ID NO:1 "can be tolerated while still maintaining the functional nucleotide phosphorylase activity" in order to make and/or use the claimed antibodies. For example, the claimed antibodies include antibodies which specifically bind to a polypeptide comprising "a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity," and to a polypeptide comprising "a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity." An assay to measure nucleotide pyrophosphohydrolase activity is disclosed in the specification at, for example, page 55, lines 22-26. One of ordinary skill in the art could routinely use the disclosed assay to identify polypeptide variants and fragments recited by the claims. One could then routinely make and/or use antibodies which specifically bind to these polypeptide variants and fragments. Contrary to the Examiner's assertions, no undue experimentation would be required.

As discussed by Brenner et al. and as cited by the Office Action, proteins of closely related functions such as hemoglobin and myoglobin have very similar structures, even when their sequences are not similar (Office Action, pages 4-5). Accordingly, proteins sharing the nucleotide pyrophosphohydrolase activity of SEQ ID NO:1 and having very high sequence similarity (at least 90%) to SEQ ID NO:1 would be even more likely to share conserved

structures. For this reason, the antibodies which specifically bound the recited variants would not be highly variant from those specifically binding to SEQ ID NO:1.

Thus, regardless of the precise functional characteristics of the SEQ ID NO:1 variants, one can still make those polypeptide variants, and antibodies which specifically bind to the variants, using the disclosure provided by the present specification. The antibodies could then be used in, for example, diagnostic testing, drug discovery, expression profiling, etc.

Furthermore, the Examiner's attention is also directed to the cited reference by Brenner et al. (*supra*). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

Claim 46 recites, *inter alia*, antibodies which specifically bind to "a polypeptide comprising . . . a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as nucleotide pyrophosphohydrolases and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "90% variants" recited by the present claims have a variation that is far less than that of all potential nucleotide pyrophosphohydrolases related to SEQ ID NO:1, i.e., those nucleotide pyrophosphohydrolases having as little as 40% identity over at least 70 residues to SEQ ID NO:1. Therefore, one would expect the SEQ ID NO:1 variants recited by the present claims to have the functional activities of a nucleotide pyrophosphohydrolase.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the

> subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any **reasons** why one would doubt that the guidance provided by the present specification would enable one to make and use the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1.

For at least the above reasons, Applicants respectfully request that this rejection be withdrawn.

Written description rejection under 35 U.S.C. §112, first paragraph

Claims 46, 48, 49, 51, 53-60, and 65-68 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being based on a specification which provides an inadequate written description of what is claimed. The Office Action appears to urge that every single member of the claimed genus of polypeptides and the antibodies which bind them must be specifically disclosed by the Specification, otherwise an inadequate written description has been set forth. However, such a disclosure is not required for an adequate written description.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or

> partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

The Office Action concurs that the specification provides adequate written description of an antibody which specifically binds the polypeptide of SEQ ID NO:1 or immunogenic fragments thereof; however, the Office Action asserts that the specification does not provide adequate written description of the antibodies to the recited variant polypeptides. The Office Action states that the specification "does not appear to have provided a description of which polypeptide sequences are "naturally-occurring," even among those polypeptides at least 90% identical to the full length sequence of SEQ ID NO:1" (Office Action, page 8). To the contrary, given the information provided by SEQ ID NO:1 (the amino acid sequence of NTPPH-2) and SEQ ID NO:2 (the polynucleotide sequence encoding NTPPH-2), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of polynucleotides encoding the recited polypeptide variants could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application, for example, at page 8, lines 9-25, page 9, lines 5-8, page 12, lines 18-26; page 14, lines 13-29 and Example VI at pages 51-53. Methods for assaying the nucleotide pyrophosphohydrolase activity of the encoded variant polypeptides are described in the specification at Example XI, page 55, lines 22-26. Conventional methods for making antibodies, such as those described at pages 30-32 of the specification, could then be used to make antibodies which specifically bind to the recited polypeptide variants.

The term "naturally occurring" is a well-known term in the art which Applicants intended to be used in such context. As such, no further definition of the term is necessary (MPEP 2163 IIA3(a)):

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of ordinary skill in the art would recognize that "***a naturally occurring amino acid sequence***" as recited in claim 46 is one which occurs in nature. Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of NTPPH-2) and SEQ ID NO:2 (the polynucleotide sequence encoding NTPPH-2), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1."

Applicants also respectfully point out that the claims are directed to antibodies, not proteins, and thus it is the properties of the antibodies, not the proteins they bind, which is relevant. The antibodies described by claim 46 specifically bind to SEQ ID NO:1, a protein that is acknowledged to be described by the specification. Nor are the antibodies of claim 46 highly variant, given that they specifically bind to naturally occurring variants having at least 90% identity to SEQ ID NO:1. As discussed above, the genus of naturally occurring polypeptides having at least 90% identity to SEQ ID NO:1 is not highly variant. As discussed above, natural selection would tend to insure that the recited variants retain the same structure as SEQ ID NO:1, so that the antibodies which specifically bound the recited variants would not be highly variant from those specifically binding to SEQ ID NO:1. For this reason, it would be clear to one of skill in the art that the specification and claims do define the structural features, or "common attributes of the genus" of the recited polypeptides that are relevant to the antibodies which bind them. The fact that the recited variants are naturally occurring also in effect imposes a structural limitation, as these variants would have been selected by nature to retain the same overall structure as SEQ ID NO:1.

For at least the above reasons, Applicants respectfully request that this rejection be

withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 46, 49, 51, 53, 54, 55, 59, 60 and 65-68 were rejected under 35 U.S.C. 102(b) as being anticipated by Cardenal et al. (Arthr. Rheum. [1996] 39(2):245-251). These rejections are respectfully traversed.

It is believed that the rejection over the Cardenal et al. document is based on a misinterpretation of the specification and the claims. The Office Action asserts that "Cardenal teaches a polyclonal antibody preparation to porcine NTPPH (page 246 in particular), a protein disclosed by the instant specification as NTPPH or NTPPH-1 (SEQ ID NO: 3; page 2, line 16 through page 3, line 13 and Figure 2 of the instant application, for example) and as being 50% identical to the NTPPH-2 of instant SEQ ID NO: 1. It is noted from the sequence alignment of Figure 3, that SEQ ID NO: 1 'has' a number of sequences in common with NTPPH taught by Cardenal." (Office Action, at page 9)

First, please note that Cardenal et al. does not teach the polypeptide sequence of NTPPH-1 or any NTPPHs. Cardenal et al. provides no recognition of such a sequence. In fact, Cardenal et al. only disclosed that all porcine tissues tested contained NTPPHase activity. Therefore, it is impossible to derive the 50% sequence identity from Cardenal. Furthermore, NTPPH-1 is a sequence identified by Incyte (Specification, page 3, lines 1-9) and not by Cardenal et al. Secondly, note that Cardenal et al. does not teach antibodies which **specifically** bind to a polypeptide comprising SEQ ID NO:1, or a naturally occurring variant thereof, the variant being ***at least 90% identical to SEQ ID NO:1*** and having ***nucleotide pyrophosphohydrolase activity***. The antibody recited in claim 46 is "An isolated antibody ***which specifically binds*** to a polypeptide comprising a polypeptide selected from the group consisting of a) a polypeptide having the amino acid sequence of SEQ ID NO:1, b) a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has nucleotide pyrophosphohydrolase activity, c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has nucleotide pyrophosphohydrolase activity, and d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." By **"specifically binding"** to SEQ ID NO:1, the

claimed antibody ***must*** bind to a polypeptide consisting of SEQ ID NO:1. The antibodies taught by Cardenal et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

Once claim 46 (and therefore claims 46, 49, 51, 53, 54, 55, 59, 60 and 65-68) has been correctly characterized and considered in its proper context, the ancillary issues regarding antibodies in composition (claims 46, 49 and 65-68), having a label (claim 51), preparing a polyclonal antibody (claims 53-55), or being produced by either a Fab expression library or an immunoglobulin expression library (claims 59-60), become moot.

For at least the above reasons, Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 46, 48 and 56-58 were rejected under 35 U.S.C. § 103(a) because the claimed antibodies are allegedly obvious over Cardenal et al. (Arthr. Rheum. [1996] 39(2):245-251) in view of Harlow et al. (in Antibodies a Laboratory Manual, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pages 72-77, 92-97, 128-135 and 141-157). This rejection is respectfully traversed.

This rejection is based on the allegation that the antibodies taught by Cardenal et al. are within the scope of the claimed antibodies. As discussed above under the previous section, the claims recite antibodies which ***specifically*** bind to a polypeptide comprising SEQ ID NO:1, or fragments or variants thereof. The antibodies taught by Cardenal et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02. Since the claim language distinguishes the recited antibodies from the teachings of Cardenal et al., the Examiner has not convincingly shown how the teachings of Cardenal et al. and/or Harlow et al. could be modified in order to arrive at the claimed subject

matter. Therefore, the Examiner has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103(a).

For at least the above reasons, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Please charge Deposit Account No. **09-0108** in the amount of **$110** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108.

Respectfully submitted,

INCYTE CORPORATION

Date: 04 April 2004

Richard C. Ekstrom
Reg. No. 37,027
Direct Dial Telephone: (650) 843-7352

Date: 5 April 2004

Yu-Mei Eureka Wang
Reg. No. 50,510
Direct Dial Telephone: (650) 621-8740

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Attachment(s):

1. the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");
2. the Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Bedilion Declaration");
3. the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and
4. Ten (10) references published before the December 22, 1997 filing date of the Magna '083

application:

a) PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995) (Reference No. 1)

b) PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995) (Reference No. 2)

c) M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (Reference No. 3)

d) PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (Reference No. 4)

e) U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996) (Reference No. 5)

f) R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (Reference No. 6)

g) PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997) (Reference No. 7)

h) Acacia Biosciences Press Release (August 11, 1997) (Reference No. 8)

i) V. Glaser, Strategies for Target Validation Streamline Evaluation of Leads, Genetic Engineering News (September 15, 1997) (Reference No. 9)

j) J. L. DeRisi et al., Exploring the metabolic and genetic control of gene expression on a genomic scale, Science 278:680 - 686 (October 24, 1997) (Reference No. 10)